DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

HFD-613

NOV 10 1998

NDA 17-447/S-054
NDA 18-655/S-032

G.D. Searle & Co.
Attention: Mr. Jerome M. Prahl
4901 Searle Parkway
Skokie, IL 60077

Dear Mr. Prahl:

Please refer to your supplemental new drug applications dated September 9, 1998, received September 10, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norpace (disopyramide phosphate) Capsules, 100 and 150 mg (NDA 17-447) and Norpace (disopyramide phosphate extended release) CR Capsules, 100 and 150 mg (NDA 18-655).

We note that these supplements were submitted as 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c) in response to our October 14, 1997 letter.

These supplemental new drug applications provide for final printed labeling revised under CLINICAL PHARMACOLOGY/Drug Interactions and PRECAUTIONS/Drug Interactions sections to reflect information regarding co-administration of disopyramide and inhibitors of cytochrome P450 3A4.

1. The following has been added at the end of the CLINICAL PHARMACOLOGY section:

> Drug Interactions
> Effects of other drugs on disopyramide pharmacokinetics: In vitro metabolic studies indicated that disopyramide is metabolized by cytochrome P450 3A4 and that inhibitors of this enzyme may result in elevation of plasma levels of disopyramide. Although specific drug interaction studies have not been done, cases of life-threatening interactions have been reported for disopyramide when given with clarithromycin and erythromycin.

2. Under PRECAUTIONS/Drug Interactions,

   a. The second paragraph has been deleted. This paragraph stated:

   > Patients taking disopyramide phosphate and erythromycin concomitantly may develop increased serum concentrations of disopyramide resulting in excessive widening of the QRS complex and/or prolongation of the Q-T interval (see Warnings). Patients taking disopyramide phosphate and hepatic enzyme inhibitors concomitantly should be closely monitored.

   b. A new third paragraph has been added to this subsection that states:

   > Although potent inhibitors of cytochrome P450 3A4 (eg, ketoconazole) have not been studied clinically, in vitro studies have shown that erythromycin and oleandomycin inhibit the

metabolism of disopyramide. Cases of life-threatening interactions have been reported for disopyramide when given with clarithromycin and erythromycin indicating that coadministration of disopyramide with inhibitors of cytochrome 3A4 could result in potentially fatal interaction.

3. Under **HOW SUPPLIED,** "Caution: Federal Law prohibits dispensing without prescription," has been changed to **"RX only."**

Your submission stated September 1998 as the implementation date for the change.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that these drug products are safe and effective for use as recommended in the final printed labeling included in your September 9, 1998 submissions. Accordingly, these supplemental applications are approved effective on the date of this letter.

At the time of your next printing, please revise "cytochrome P450 3A4" and "cytochrome 3A4" to state "CYP3A4." This request is based on the finalization of the nomenclature for cytochromes P450 and should be reported in your next annual report.

In addition, please update the Division within the next six months about the status of in vitro studies aimed at identifying the CYP isozymes involved in the metabolism of disopyramide.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Diana Willard
Regulatory Health Project Manager
(301) 594-5311

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
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